How Model-Based Meta-Analysis Leverages Public Data to Support Strategic Drug Development Decision Making

Using public preclinical and clinical data can shorten drug development and decrease costs.

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Why Conduct a Model-Based Meta-Analysis (MBMA)?

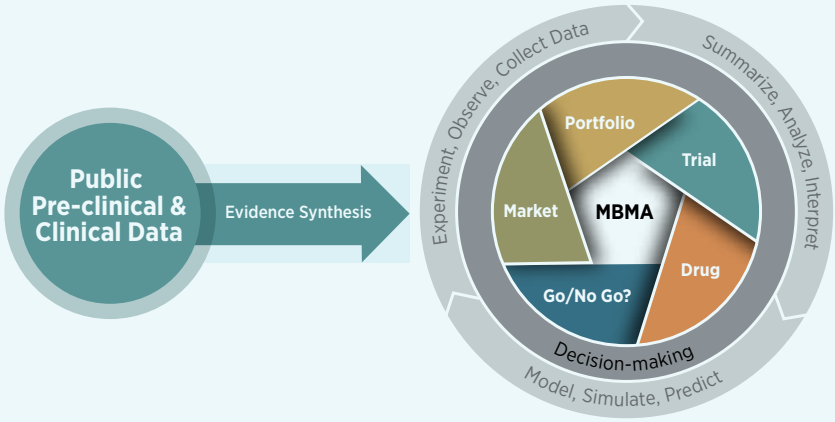
MBMA represents a smart, quantitative approach to enable a sponsor to supplement its existing proprietary drug data with public preclinical and clinical data, allowing it to make more informed strategic drug development decisions.

MBMA involves the systematic search and tabulation of summary results from external data sources and their combination with in-house clinical trial data to create a richer resource. The resulting highly curated data can be used with parametric pharmacology models to increase drug development productivity, inform portfolio management, and improve clinical trial success.

MBMA can be applied in most established therapeutic areas, ranging from oncology through metabolic diseases such as diabetes to cardiovascular and kidney disease. The primary limiting factor is the richness of the available literature, which is generally only an issue with newly emerging fields.

About 70 percent of the work involved with MBMA is in extracting all the relevant information from the literature or clinical trial registries and then formatting and preparing it for analysis. The extracted information must first be turned into a tabular, analyzable form. Then, it needs to be harmonized because two endpoints might have similar naming conventions but very different interpretations or definitions across therapeutic areas. Those steps have to be completed before the data can be analyzed with a parametric model.

Figure 1
The impact of leveraging public drug data to augment the proprietary data that sponsors generate during each cycle.



Historical Context

In its earliest form, known as pairwise meta-analysis, this type of assessment allowed data from multiple clinical trials comparing Drug A to Drug B to be combined, after the observations were weighted to reflect sample size and variability.

Later, network meta-analysis permitted bridging between two treatments that had never been studied together in the same trial, after making appropriate assumptions about consistency across trials. For example, Drugs A and C could be compared effectively by using literature data from studies of Drug A with B and Drug B with C, using Drug B as the bridge.

MBMA functions as an extension of network meta-analysis because it not only allows comparing treatments that have not been studied together in a clinical trial, but it also adds pharmacological data, such as dose-response relationships and time dependencies to the mix.

MBMA allows drawing conclusions about how a new drug candidate will perform relative to the existing standard of care and other new compounds under development—vitally important information when considering a go/no-go decision for a portfolio compound. It also enables clinical trial design and dosing regimen to be optimized based on safety and efficacy results demonstrated in a broad range of studies. Not only can this approach help to maximize the treatment effect in the new trial, but it may also result in shorter trials with fewer patients.

MBMA is a highly flexible approach. It can be used to compare drugs in the same or multiple therapeutic classes, optimize clinical trial designs, predict long-term responses based on short-term endpoints or biomarkers, and potentially be used to guide dosing recommendations for unstudied indications or populations. It can also be used to assess the impact of the placebo response, a very important differentiator, especially in trials for pain medications. Several of these examples are described in more detail later in this article.

Impact of MBMA

Sponsors invest large quantities of money, time, and resources into developing their own proprietary drug data. It is a cycle that continues throughout the drug development process. Sponsors design an experiment or trial, conduct it, analyze the results, and then use that information to make an inference about their drug candidate. That newfound knowledge is then incorporated into the next trial and the cycle is repeated until sufficient data have been gathered to support a new drug or biologics license application. Every cycle is expensive.

By using public preclinical and clinical drug data to supplement the sponsor's own proprietary data, MBMA can fill in some of the knowledge gaps, helping to shorten the drug development process and reduce costs. It also enables more complete clinical trial efficacy, tolerability, and safety data to be employed to inform strategic drug development decisions.

Figure 2
Competitive plot showing 57 drugs from nine therapeutic classes.

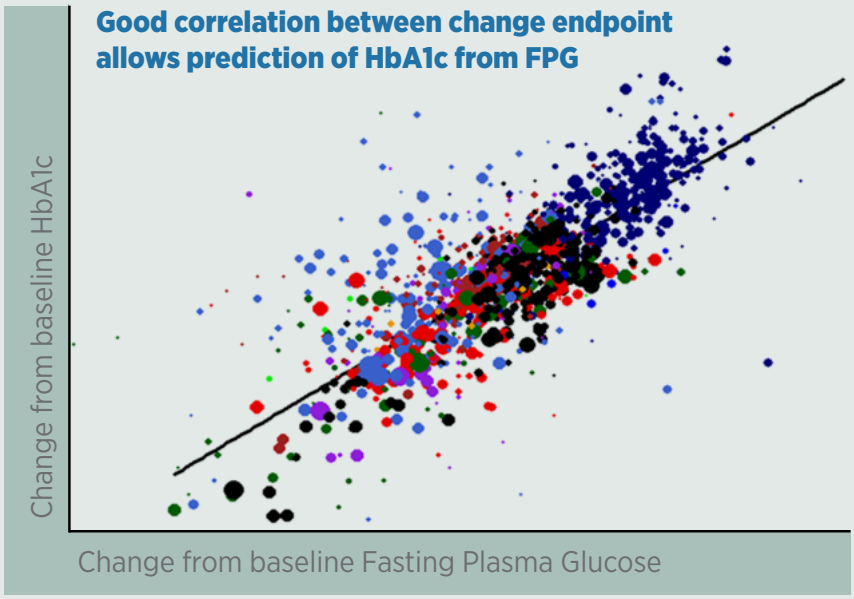
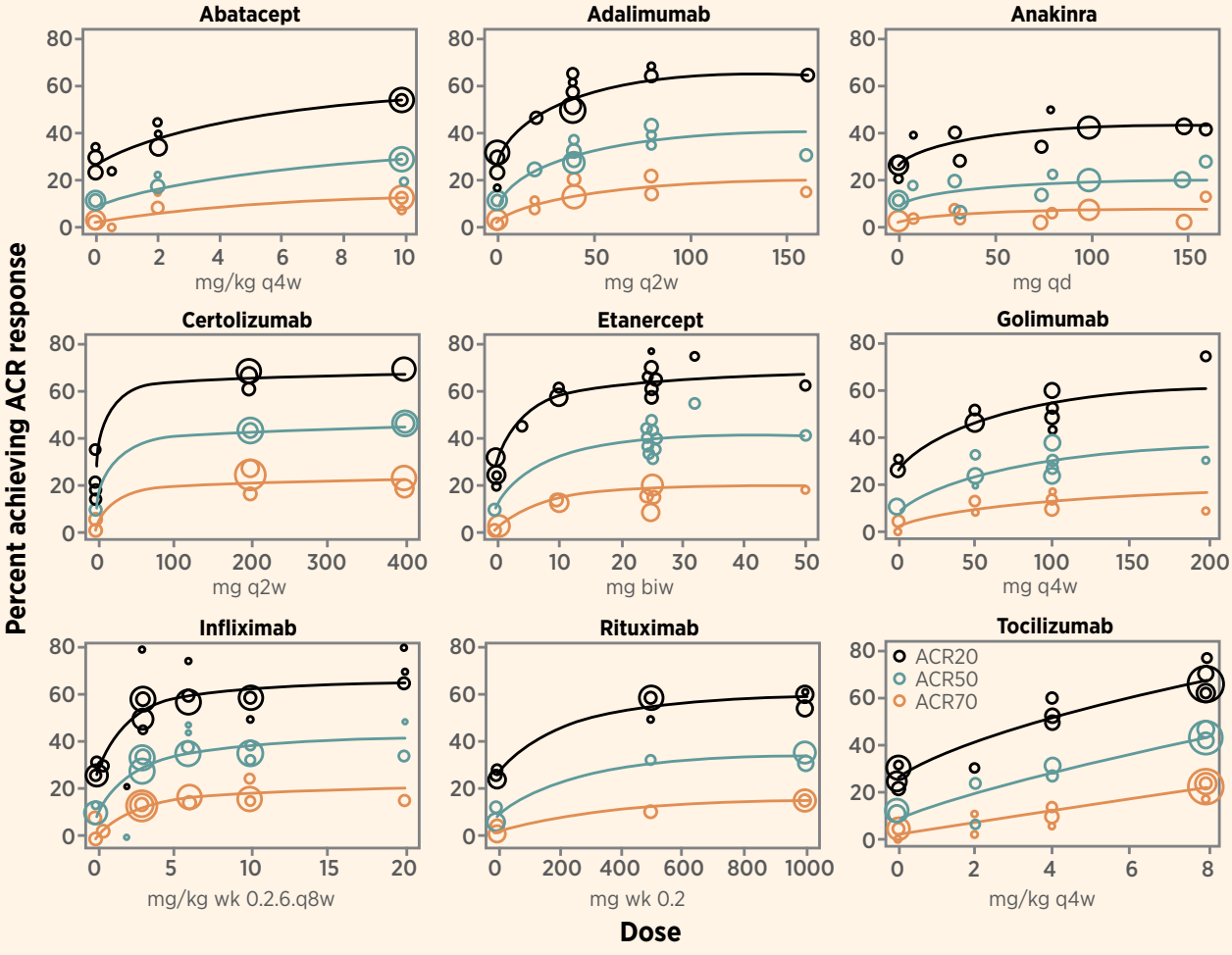


Figure 3
Rheumatoid arthritis study.[3] *Used with permission.*



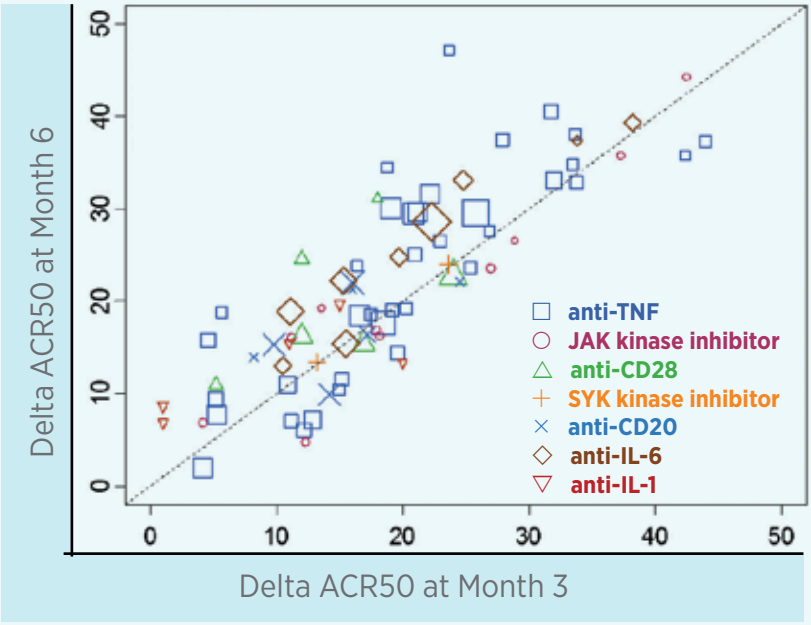
Cost Saving Approach

Here is a brief example that illustrates how MBMA increases knowledge while saving money. If one assumes that it costs about $200 million to develop an antidiabetic therapy, then it would cost a sponsor about $7 billion to generate all the data that are shown in this competitive plot because it includes 57 drugs from nine therapeutic classes.

The colors in this plot represent different classes of antidiabetic therapies, and the hemoglobin A1c (HbA1c) test shows what the average amount of glucose attached to hemoglobin has been over the past three months.[1]

This plot shows that HbA1c, the longer responding endpoint, is highly correlated with fasting plasma glucose (FPG) response, which is a very rapidly responding biomarker.

Figure 4
Rheumatoid arthritis short- v. long-term effects.[4] *Used with permission*



Furthermore, this relationship seems to remain consistent across the various therapeutic classes. Therefore, HbA1c can be largely predicted based on a short-term FPG response, even for novel therapeutic classes.

While a sponsor would be unlikely to invest $7 billion to determine the impact of 57 antidiabetic therapies on HbA1c levels, this conceptual example shows how MBMA can provide real value.

Pioneering Paper

The first MBMA paper, which featured a rheumatoid arthritis study by Mandema et al, was published in 2011.[2] Their analysis permitted comparing rheumatoid arthritis drugs and regimens that had never been studied together in the same trial.

The dataset included 50 trials, more than 21,000 patients, and five classes of disease-modifying anti-rheumatic drugs, with an emphasis on monoclonal antibodies. Therefore, competitive comparisons could be made across several drugs.

Their model took a dose response approach with ACR20, 50, and 70 responses described simultaneously. ACR20, 50 and 70 are standardized American College of Rheumatology improvement criteria used to measure responses in rheumatoid arthritis trials. Each end point represented a different level of response. ACR70 represented a 70 percent reduction from baseline in the ACR score; therefore it was the most stringent and least likely to occur.

The relationship between the ACR20 and ACR50 response proved to be predictable and consistent across drug classes. This analysis focused on responses at 12 weeks and later, when it was assumed that the disease and drug response would be fairly stable.

Predicts Long-term Responses Based on Short-term Ones

In a 2016 rheumatoid arthritis paper, Wang et al used MBMA to examine the relationship between short- and long-term treatment effects.[4] The team constructed a database using information from 68 reported clinical trials and employed it to develop a generalized nonlinear model to quantify the relationship between three- and six-month ACR50 treatment effects and test the impact of covariates. Their research showed that an ACR50 response at three months was a strong predictor of ACR50 response at six months.[4]

The value proposition for this MBMA is clear. If a sponsor can use three-month data to predict six-month efficacy, it can shorten its clinical trial, saving time and resources, and make the go/no-go decision on its drug candidate significantly earlier.

Supports Indication Hopping

MBMA can also be used to support indication hopping. For example, if a sponsor has received regulatory approval for a drug to treat psoriasis, the company might want to seek follow-on approval for additional related indications, such as psoriatic arthritis or ankylosing spondylitis. One of the key decisions that needs to be made during indication hopping is whether the dose needs to be adjusted for the new indication.

Ankylosing spondylitis is a form of chronic inflammatory arthritis that primarily affects the spine,[5] according to the National Institutes of Health. Over time, back movement gradually becomes limited as the vertebrae fuse together.

In this case, a literature database can be developed for related psoriasis therapies and one or both follow-on indications. Relative drug potencies in each indication can be characterized through an MBMA that jointly fits data from psoriasis, psoriatic arthritis, and ankylosing spondylitis trials. Potency estimates for related therapies provide dose scaling factor(s) for the new indications.

In the case of psoriasis and psoriatic arthritis, there is often a shared endpoint—the Psoriasis Area Severity Index score—that is reported in both types of trials, even though it is probably not the endpoint of primary interest with psoriatic arthritis. This shared information permits bridging across endpoints, allowing a dose response model to be developed that describes the key endpoints across all three indications and enables formal testing of whether there are differences in potency across those indications.

The sponsor's planned dose regimens for psoriatic arthritis and ankylosing spondylitis indications can then be examined in context with the drug's dose response for psoriasis.

Evaluates Placebo Effect

Studies of central nervous system diseases are plagued by significant placebo effects. Compounding that problem, the placebo response has gotten larger with time. A 2015 meta-analysis that examined 84 neuropathic pain randomized control trials conducted between 1990 and 2013 found that placebo responses in this therapeutic area have increased dramatically, while drug responses have stayed the same.[6] Measuring drug effectiveness above the placebo effect is a major hurdle for sponsors.

In the 2018 study by Arrington et al, MBMA enabled a quantitative model to be developed which compared treatment effects for drugs commonly used to treat neuropathic pain caused by diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PN), and fibromyalgia.[7] The dataset included information on 21 drugs and three combined therapies across nine drug classes.

The goal was to develop a joint response model, which described the proportion of patients who achieved a ≥30 percent Pain Intensity Difference (PID) reduction (PID30) and ≥50 percent reduction (PID50) in pain score from baseline.

Data were included from 74 randomized controlled trials involving more than 26,000 patients. There were 38 trials in DPN, 15 in PN, and 21 in fibromyalgia. Of those, 61 trials measured PID30, 66 had PID50, and 53 had both PID30 and PID50.

One might have thought that different neuropathic indications have comparable placebo responses. However, the study demonstrated a lower placebo response for fibromyalgia (29.9 percent) than for DPN (37.1 percent) and PN (37.1 percent), and a decrease in treatment effect with increasing placebo response. Thus, sponsors have a higher barrier to surmount for DPN and PN than fibromyalgia to show efficacy above the placebo response.

The resulting MBMA allowed researchers to compare the observed and model-predicted dose-response for a subset of drugs included in the analysis. It confirmed that MBMA can provide a quantitative framework for comparing investigational new compounds with the standard of care for neuropathic pain. This framework can be used to predict the likelihood that a new drug will show efficacy above the placebo response. Lastly, it improved researchers' understanding of the drug-response relationship for compounds used to treat different types of pain.

Conclusion

MBMA provides a reliable, quantitative framework within which sponsors can compare public preclinical and clinical data with their own proprietary data about their drug. It is a highly efficient and effective approach, which makes the best combined use of all the available safety, efficacy, and competitive market data. Consequently, MBMA helps sponsors to make the wisest, most informed decisions about the next steps in their drug's development and market positioning.

Certara maintains 40 curated databases of clinical drug efficacy and safety data from the published biomedical literature for different diseases to support MBMA.

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